Remarks

The Amendments to the Claims

Claim 60 has been amended to recite a hypermutable, transgenic mouse wherein "germ and somatic" cells comprise a dominant negative allele of a *PMS2* mismatch repair (MMR) gene. The amendment is supported by the specification which discloses the following as methods of producing transgenic animals:

> Any method for making transgenic animals known in the art can be used. According to one process of producing a transgenic animal, the polynucleotide is injected into a fertilized egg of the animal and the injected egg is placed into a pseudo-pregnant female. The egg develops into a mature animal in which the polynucleotide is incorporated and expressed. The fertilized egg is produced in vitro from the egg and the sperm of donor animals of the same species as the pseudo-pregnant female, who is prepared by hormone treatments to receive the fertilized egg and become pregnant. An alternative method for producing transgenic animals involves introducing the polynucleotide into embryonic cells by injection or transfection and reintroducing the embryonic cells into the developing embryo.

Page 9, lines 21-31. These methods produce a transgenic animal having germline and somatic cells comprising the transgene. Thus, the specification discloses production of a transgenic animal in which some or all of its cells comprise a transgene.

Claim 60 has also been amended to recite that the dominant negative allele of the PMS2 mismatch repair gene comprises "a *PMS2-134* allele" in place of a "truncation mutation." The amendment is supported by the specification which discloses, "Dominant negative alleles of a mismatch repair gene can be obtained from the cells of humans, animals, yeast, bacteria, or other organisms . . . Dominant negative alleles of a mismatch repair gene can also be created artificially, for example, by producing variants of the *hPMS2-134* allele or other mismatch repair

genes." Page 7, lines 13-23. Claims 61 and 71 have been similarly amended and are similarly supported by the specification.

New claims 88 and 91 recite that the mismatch repair gene is human *PMS2*. New claims 89 and 92 recite that the mismatch repair gene comprises a truncation mutation at codon 134 as shown in SEQ ID NO: 1. New claims 94-96 recite a mouse or mouse egg comprising a protein consisting of the first 133 amino acid residues of human PMS2. These claims are supported by the specification which discloses, "An example of a dominant negative allele of a mismatch repair gene is the human gene hPMS2-134, which carries a truncation mutation at codon 134." Page 7 lines 2-4. SEQ ID NO: 1 is the amino acid sequence of human *PMS2*.

New claims 90 and 93 recite that the truncation mutation is a thymidine at nucleotide 424 of wild-type *PMS2* as shown in SEQ ID NO: 1. This amendment is supported by claim 83 which recites that the truncation mutation is a thymidine at nucleotide 424 of wild-type *PMS2* as shown in SEQ ID NO: 1.

None of these amendments introduce new matter.

The Rejection of Claims 60-62, 70-75, and 81-87 Under 35 U.S.C. § 112, ¶ 1

Claims 60-62, 70-75, and 81-87 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled for their full scope. Claim 70 has been canceled. Applicants respectfully traverse the rejection as applied to claims 60-62, 71-75, and 81-87.

The rejected claims are directed to transgenic mice comprising a dominant negative allele of a *PMS2* mismatch repair gene which comprises a *PMS2-134* homolog and methods of making and using such mice.

To comply with the enablement requirement, one of skill in the art must be able to make and use the entire scope of the claimed invention without resorting to undue experimentation. *In re Wright*, 999 F.2d 1561 (Fed. Cir. 1993). See also M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. M.P.E.P. § 2164.03. In fact, what is well known in the art need not be disclosed and is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). See also M.P.E.P. § 2164.08.

The final Office Action asserts that claims 60-62, 71-75, and 81-87 are not enabled for their full scope. "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Final Office Action at page 3, lines 2-5. The final Office Action asserts that the claims are not enabled across their full scope for the following reasons:

- the claims encompass, but are not enabled for, *any* truncation mutation of *any* dominant negative allele of a *PMS2* mismatch repair gene;
- the specification does not provide guidance as to the phenotype of the transgenic mice; and
- the technology of producing transgenic mice was unpredictable.

Final Office Action at page 3 line 24 to page 4, line 3. Each of these reasons will be discussed in turn.

Any truncation mutation of any dominant negative allele of a *PMS2* mismatch repair gene

Independent claims 50, 61, and 71, have been amended to recite that the transgenic mouse comprises a dominant negative allele of a *PMS2* mismatch repair gene comprising a "*PMS2-134* homolog" in place of a "truncation mutation." One of skill in the art would be able to make and use transgenic mice comprising a *PMS2-134* homolog without resorting to undue experimentation.

It would have been predictable that *PMS2-134* homologs would induce hypermutability in transgenic mice. Applicants have submitted evidence that human and *Arabidopsis thaliana PMS2* homologs both induce hypermutability when expressed in cells. The declaration of Dr. Nicholas Nicolaides, of record, provides evidence that both human and *A. thaliana PMS2-134* homologs induced a hypermutable phenotype in bacteria. See paragraph bridging pages 2 and 3. That *PMS2-134* homologs from widely disparate species such as human and *A. thaliana* induce hypermutability in a further disparate organism, bacteria cells, evidences that there is strong conservation of the mismatch repair pathway among species ranging from bacteria to plants to mammals. Furthermore, the human and *A. thaliana* PMS2-134 polypeptides share 65.1% amino acid sequence similarity and 50.7% amino acid sequence identity. See Figure 1 legend attached to declaration. Because these *PMS2-134* homologs are capable of inducing a hypermutable phenotype in cells, it would be predicted that *PMS2-134* homologs from other species would be capable of inducing a hypermutable phenotype as well.

Applicants have also provided guidance for identifying further *PMS2-134* homologs that exert a dominant negative effect upon mismatch repair. The specification teaches that cells

comprising a dominant negative allele of a MMR gene can be identified "by testing the mismatch repair activity caused by the allele in the presence of one or more wild-type alleles." Page 7, lines 25-27; see also page 10, lines 15-24. One of skill in the art would have been able to perform such tests on cells comprising a putative *PMS2-134* homolog. The declaration of Dr. Nicholas Nicolaides provides evidence that one of skill in the art would be able to identify *PMS2-134* homologs having a dominant negative effect on MMR without resorting to undue experimentation. The declaration establishes that simple alignment of the human and *Arabidopsis thaliana PMS2* cDNA sequences identified an *A. thaliana PMS2-134* homolog. See paragraph bridging pages 1 and 2. The declaration further provides evidence that the identified *A. thaliana PMS2-134* homolog induced a hypermutable phenotype in bacteria. See paragraph bridging pages 2 and 3. One of skill in the art would have been able to identify additional dominant negative alleles of a *PMS2* mismatch repair gene comprising a *PMS2-134* homolog without resorting to undue experimentation.

Enablement requires that the ordinarily skilled artisan be able to make and use the invention without undue experimentation. Because human and plant *PMS2-134* homologs produce a hypermutable phenotype in cells, one of skill in the art would have expected *PMS2-134* homologs of other species to have a similar effect. To identify other *PMS2-134* homologs and to substitute *hPMS2-134* with other *PMS2-134* homologs in the production of a transgenic mouse would have been merely routine to one of skill in the art using the specification and the knowledge in the art. Applicants have taught how to make and use a hypermutable, transgenic mouse having a dominant negative allele of a *PMS2* mismatch repair gene comprising a *PMS2-134* homolog without resorting to undue experimentation. Applicants have thus enabled the full scope of the claimed invention.

The phenotype of the transgenic mice

The final Office Action asserts that "applicants' specification does not provide any guidance as to what would be the phenotype of such mice and therefore, an artisan would not know how to use these mice." Final Office Action at page 3, lines 26-28. The specification, however, does disclose the phenotype of the claimed mice at page 7, lines 28-31: "A cell or an animal into which a dominant negative allele of a mismatch repair gene has been introduced will become hypermutable. This means that the spontaneous mutation rate of such cells or animals is elevated compared to cells or animals without such alleles." The claims also recite a "hypermutable, transgenic mouse." Applicants have further provided evidence that the phenotype of the transgenic mice is their elevated rate of mutation relative to animals without a dominant negative allele of a mismatch repair gene. Applicants submitted a first declaration of Dr. J. Bradford Kline, executed September 16, 2002, describing the production of transgenic mice comprising a dominant negative allele of human *PMS2* (*hPMS2-134*) using methods described in the specification. Applicants submitted a supplemental declaration of Dr. J. Bradford Kline, executed April 17, 2003, describing the hypermutable phenotype of the transgenic mice. Applicants have therefore guided one of skill in the art as to the phenotype of the claimed transgenic mice.

Unpredictability of transgenic technology

The final Office Action asserts that "in view of the unpredictability of the transgenic technology, an artisan would not have been able to make such transgenic mice without undue experimentation." Final Office Action at page 4, lines 1-4. Contrary to the assertion in the final

Office Action, the technology of producing transgenic mice was predictable at the time the application was filed. The specification provides guidance to one of skill in the art such that he or she would be able to make and use transgenic mice comprising a dominant negative *PMS2* allele. The specification discloses that methods of making transgenic animals were known as of the application filing date and briefly describes methods of making such transgenic animals. The specification discloses:

> Any method for making transgenic animals known in the art can be used. According to one process of producing a transgenic animal, the polynucleotide is injected into a fertilized egg of the animal and the injected egg is placed into a pseudo-pregnant female. The egg develops into a mature animal in which the polynucleotide is incorporated and expressed. The fertilized egg is produced in vitro from the egg and the sperm of donor animals of the same species as the pseudo-pregnant female, who is prepared by hormone treatments to receive the fertilized egg and become pregnant. An alternative method for producing transgenic animals involves introducing the polynucleotide into embryonic cells by injection or transfection and reintroducing the embryonic cells into the developing embryo.

Page 9, lines 21-31. One of skill in the art would have been able to produce transgenic mice based on the disclosed methods provided in the specification.

Furthermore, as indicated in the specification, the art had developed methods of predictably producing transgenic mice prior to the effective filing date of the application, April 14, 1998. U.S. Patent No. 6,339,183 (filed November 1997), of record, teaches production of a transgenic mouse expressing a uroplakin II gene. See Example 2 at column 9, line 7 to column 10, line 5. U.S. Patent No. 5,965,788 (filed June 1992), of record, teaches production of transgenic mice expressing human growth hormone. See Example 3 at column 7, lines 10-35. U.S. Patent No. 5,912,411 (filed June 5, 1995), of record, teaches production of transgenic mice expressing the luciferase gene. See Example 6 at column 52, line 10 to column 54, line 2. In

fact, laboratory manuals teaching how to produce a transgenic mouse had been published prior to the effective filing date of the application. One such manual is entitled "Manipulating the Mouse Embryo, A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1986, ed. Hogan, Costantini, and Lacy. Thus there was a high degree of predictability in the art for methods of producing transgenic mice.

Given the high level of predictability in the art of producing transgenic mice and the direction supplied in the application, one of skill in the art would have been able to make and use a transgenic mouse without recourse to undue experimentation.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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